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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/561,951	11/21/2006	**Yannick Guilloux**	283632US0XPCT	8052

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EXAMINER	
DUFFY, BRADLEY	
ART UNIT	**PAPER NUMBER**
1643	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/561,951	GUILLOUX ET AL.	
	Examiner	Art Unit	
	BRADLEY DUFFY	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *1,4,6-12 and 14-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,5 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 December 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/14/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Nottice to comply, Exhibts A, B.

DETAILED ACTION

1. The amendment filed October 6, 2008, is acknowledged and has been entered. Claims 1, 2 and 11 have been amended.

2. The election with traverse filed May 30, 2008, is acknowledged and has been entered.

Applicant has elected the invention of Group LXVIII, claims 2, 3, 5 and 13, drawn to a peptide that comprises a fragment of 8-11 consecutive amino acids of the MMP-2 metalloprotease and compositions comprising such a peptide and an adjuvant.

3. Claims 1-19 are pending. Claims 1, 4, 6-12 and 14-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply May 30, 2008.

4. Claims 2, 3, 5 and 13 are under examination.

Election/Restrictions

5. Applicant's traversal of the restriction and election requirement set forth in the Office action mailed April 1, 2008, is acknowledged.

Applicant's arguments have been carefully considered but have not been found persuasive for the following reasons:

The traversal is "on the grounds that no adequate reasons and/or examples have been provided to support a conclusion of patentable distinctiveness between the identified groups. Also, it has not been shown that a burden exists in searching the claims of the several groups".

In response, this argument is not found persuasive because this

application is a National Stage entry of PCT/FR04/01585 and unity of invention (not restriction practice pursuant to 37 CFR 1.141 -1.146) is applicable in national stage applications submitted under 35 U.S.C. 371. See MPEP 1893.03(d) Notably, PCT Rule 13.1 sets froth that unity of invention shall be fulfilled only when the inventions are linked by a special technical feature that defines a contribution over the prior art. See MPEP 1850

However, in this case, as set forth in the pervious office action, the groups are not linked by a special technical feature and Applicant has provided no evidence or arguments as to why the groups share a special technical feature or why the requirement for restriction in this National Stage entry is improper.

Therefore, for these reasons and the reasons set forth in the Office action mailed April 1, 2008, the inventions do not share unity of invention as required under PCT Rule 13 and the restriction/election requirement is deemed proper and therefore made FINAL.

Information Disclosure Statement

6. The references cited in the information disclosure statement filed on March 14, 2006, have been considered. Notably, while considered, the US applications were crossed out as they do not conform with the information disclosure statement requirements because, for example, the information disclosure statement does not establish these applications as publicly available documents (see MPEP 609).

Priority

7. Applicant's claim under 35 USC §§ 119 and/or 120 for benefit of the earlier filing date of the foreign application France 03/07659 filed June 25 , 2003, is acknowledged.

In this case, while a certified copy of foreign application France 03/07659 has been placed of record in the file, Applicants have not provided a verified or certified translation of document France 03/07659. Therefore, the effective filing

date of the instant claims is the filing date of PCT/FR04/01585, i.e., June 24, 2004. See 37 CFR 1.55. See MPEP § 201.15.

Notably, when Applicant relies upon a document in a language other than English 37 CFR § 41.154 states:

> When a party relies on a document or is required to produce a document in a language other than English, a translation of the document into English and an affidavit attesting to the accuracy of the translation must be filed with the document.

Additionally, the claims do not properly benefit under 35 U.S.C. §§ 119 and/or 120 by the earlier filing dates of the priority documents claimed, since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure.

Accordingly, the effective filing date of the claims is deemed the filing date of filing date of PCT/FR04/01585, i.e., June 24, 2004.

Drawings

8. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference character(s) not mentioned in the brief description of the drawings: Figure 1, Figure 2, Figure 3 and Figure 4. In this case, the specification lacks a brief description of the drawings entirely. Corrected drawing sheets in compliance with 37 CFR 1.121(d), or amendment to the specification to add the reference character(s) in the description in compliance with 37 CFR 1.121(b) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

9. The disclosure is objected to because of the following informalities:

a. The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

An example of such an improperly demarcated trademark appearing in the specification is Fast Track™ (see, e.g., page 10).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at <http://www.uspto.gov/web/menu/search.html>.

b. The disclosure is objected to because the disclosure refers to embedded hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified. Reference to hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified is impermissible and therefore requires deletion.

Examples of such impermissible disclosures appear in the specification at page 5.

The attempt to incorporate essential or non-essential subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP § 608.01(p), paragraph I regarding acceptable incorporation by reference. See 37 CFR § 1.57.

c. The abstract of the disclosure is objected to because for the recitation of the legal terminology "said peptides". See MPEP § 608.01(b).

d. The specification is objected to because it fails to comply with the requirement set forth under 37 C.F.R. §§ 1.74 and 1.77. In this case, the specification lacks a "Brief Description of Drawings" section in accordance with the requirement of § 1.77, which describes the drawings in accordance with § 1.74. See M.P.E.P. § 608.01(a) and (f).

e. The specification contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). Sequences appearing in the specification and/or drawings must be identified by sequence identifier in accordance with 37 C.F.R. 1.821(d). According to 37 CFR § 1.821(a), an unbranched sequence of four or more specifically identified amino acids or an unbranched sequence of ten or more nucleotides must be identified by sequence identification numbers. See MPEP § 2422.01.

In this instance, the there are amino acid sequences on pages 12 and 13 that are not identified by sequence identification numbers. Applicant must provide appropriate amendments to the specification inserting the required sequence identifiers. In this case, these amino acid sequences appear to be in the sequence listing as filed.

As noted in the attached Notice to Comply, appropriate action correcting this deficiency is required. If necessary to correct the deficiency, Applicant must submit paper and computer-readable copies of a substitute sequence listing, together with an amendment directing its entry into the specification and a statement that the content of both copies are the same and, where applicable, include no new matter.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

10. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

11. Claim 2 and 3 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Due to the indefinite nature of the claims as detailed below, they are broadly, but reasonably interpreted to include any peptide comprising the sequence of GLPPDVQRV, such as any human MMP-2 peptide which comprises such a sequence, which are naturally occurring and comprised within an organism, including a human. As such, absent a showing of any difference, the claims encompass naturally occurring polypeptides.

In the absence of the hand of man, the naturally occurring polypeptides are considered non-statutory subject matter. See *Diamond v. Chakrabadv*, 206 U.S.P.Q. 193 (1980)).

This issue may be remedied by amending the claims to recite a limitation requiring the "immunogenic peptide" to be "isolated".

Claim Rejections - 35 USC § 112

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 2, 3, 5 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 2, 3, 5 and 13 are indefinite because claim 1 recites "an immunogenic peptide **comprising** a T epitope presented by MHC I, that **consists of** a fragment of 8 to 11 consecutive amino acids ...". Notably, a broad range or limitation together with a narrow range or limitation that falls within the

broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, it is unclear whether the peptide itself consists of 8-11 consecutive amino acids, or rather the T epitope presented by MHC I consists of 8-11 consecutive amino acids which makes it unclear what the metes and bounds of the invention is intended to be. Accordingly, due to the ambiguity that results from a broad limitation followed by a narrow limitation used in claim 1, the claims fail to delineate the metes and bounds of the subject matter regarded as the invention with the clarity and particularity necessary to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, so as to permit the skilled artisan to know or determine infringing subject matter.

(b) Claims 2, 3, 5 and 13 are further indefinite because claim 1 recites “which is capable of inducing a cytotoxic T lymphocyte response against tumor cells expressing MMP-2“. Notably, this recitation renders the claims indefinite because it is unclear if the peptide, the T epitope, the fragment of the MMP-2 metalloprotease or the MMP-2 metalloprotease itself must be capable of inducing a cytotoxic T lymphocyte response. Without knowing what is intended to be capable of inducing a cytotoxic T lymphocyte response the claims cannot be construed unambiguously. Accordingly, due to the ambiguity that results from this recitation, the claims fail to delineate the metes and bounds of the subject

matter regarded as the invention with the clarity and particularity necessary to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, so as to permit the skilled artisan to know or determine infringing subject matter.

(c) Claim 3 is further indefinite for reciting "the fragment comprises the sequence GLPDVQRV (SEQ ID NO:1)" In this case the amino acid sequence of SEQ ID NO:1 is 9 amino acids in length, and since the fragment comprises this amino acid sequence, while claim 2 sets forth "a fragment of 8 to 11 consecutive amino acids" it is unclear how a fragment that consists of 8 amino acid residues might comprise the amino acid sequence of SEQ ID NO:1 which is 9 amino acids in length. Accordingly, the fragment set froth in claim 3 lacks antecedent basis in claim 2 and it is submitted that this claim fails to delineate the metes and bounds of the subject matter that Applicant regards as the invention with the requisite clarity and particularity to permit the skilled artisan to know or determine infringing subject matter.

(d) Claims 2, 3, 5 and 13 are indefinite because of the use of the terminology "MMP-2 metalloprotease" or "MMP-2", as the sole means to identify the protein from which a fragment of 8-11 amino acids is from or which is expressed by tumor cells. The use of such laboratory designations to identify a protein renders the claim indefinite because different laboratories may use the same nomenclature to identify structurally and/or functionally distinct proteins, such as, e.g., orthologs, paralogs, homologs or splice variants that are perhaps produced by different types of cells, tissues, or animals (including, e.g., human, horse, cow, pig, mouse, rat, frog, etc.), or perhaps proteins that are all together different and lack any apparent structural or functional relationship.

This position is supported by the results of a search of the protein database available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Protein using "MMP-2" as the search query. This search identified multiple different proteins from different species, each of which perhaps describes a protein that is commonly designated "MMP-2" and it is unclear to which one(s) the claims refer. Notably, the search further identified two distinct human variants designated

MMP-2 one of which has a sequence of 660 amino acids, while the other has a sequence of 610 amino acids. Furthermore, because of the inconsistent use of "MMP-2 metalloprotease" or "MMP-2" in claim 2, it is unclear if the MMP-2 expressed by tumor cells is that same or different from the "MMP-2 metalloprotease" previously referred to. Accordingly, because it is unclear or cannot be ascertained to which of the different proteins termed "MMP-2" the claims are directed, it is submitted that the metes and bounds of the subject matter that is regarded as the invention is not delineated with the clarity and particularity to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, so as permit the skilled artisan to know or determine infringing subject matter.

Therefore, these claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 2, 3, 5 and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written

description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines" continue:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

With further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention*.

In the instant case, the claims are broadly drawn to a structurally and functionally diverse genus of "immunogenic peptides comprising a T epitope

presented by MHC I, that consists of a fragment of 8-11 consecutive amino acids of a structurally and functionally diverse genus of "MMP-2 metalloproteases" which is capable of inducing a cytotoxic T lymphocyte response against tumor cells expressing "MMP-2"". (see e.g., claim 1). Notably, due to the indefinite nature of a broad limitation followed by a narrow limitation detailed above, the claims are herein broadly, but reasonably drawn to any immunogenic peptide comprising a T epitope, wherein the T epitope consists of a fragment of 8-11 consecutive amino acids. Furthermore, claim 2 is *herein* drawn to any immunogenic peptide comprising a T epitope, wherein the T epitope comprises the amino acid sequence of SEQ ID NO:1.

As such the claims are directed to a genus of structurally disparate peptides that are merely described as comprising a fragment of 8-11 consecutive amino acids of a structurally and functionally diverse genus of "MMP-2 metalloproteases" or to such structurally disparate peptides comprising the amino acid sequence of SEQ ID NO:1.

However, in this case the specification only provides evidence that a 9 amino acid immunogenic peptide consisting of the amino acids sequence of SEQ ID NO:1 is presented by HLA-A*0201 and is capable of inducing a specific CTL response with respect to HLA-A*0201 melanoma cells expressing an MMP-2 antigen (see e.g., page 4). Therefore, it is submitted that specification does not describe a correlation between any particularly identifying (i.e., substantial) structural feature that describes the genus of "peptides having a fragment of 8-11 consecutive amino acids of a structurally and functionally diverse genus of "MMP-2 metalloproteases" or "such peptides comprising the amino acid sequence of SEQ ID NO:1", which are capable of inducing a cytotoxic T lymphocyte response against tumor cells expressing MMP-2. Notably, while the peptide consisting of the amino acid sequence of SEQ ID NO:1 is presented by the HLA-A*0201 MHC class I molecule, one of skill in the art would not consider such a peptide representative of the claimed genus of peptides that comprise additional amino acids or comprise an altogether different sequence of 8-11

consecutive amino acids of a structurally and functionally diverse genus of "MMP-2 metalloproteases" because one of skill in the art would not be able to immediately envision, predict or recognize which of the other "peptides" would bind to class I MHC molecules or would be capable of inducing a cytotoxic T lymphocytic response against tumor cells expressing MMP-2. This is the case because the specification does not provide sufficient guidance or direction that would allow one of skill in the art to immediately envision, recognize or predict which peptides comprising 8-11 amino acids of MMP-2 or which peptides comprising the amino acid sequence of SEQ ID NO:1 would be capable of inducing a cytotoxic T lymphocyte response against tumor cells expressing MMP-2. For example, while the specification teaches that melanoma cells lines that express a MMP-2 polypeptide which is 661 amino acids in length according to Figure 3 are recognized by cytotoxic T lymphocytes that are reactive with the peptide consisting of the amino acid sequence of SEQ ID NO:1, these same cytotoxic T lymphocytes fail to recognize other tumor cells expressing a MMP-2 polypeptide (see e.g., page 14).

Furthermore, Elgert et al (Immunology: Understanding the Immune System, 1996, pages 143-145) teach that MHC class I molecules bind peptide antigens originating in cells that consist of 9-11 amino acids, so it is submitted that so one of skill in the art could not immediately envision, recognize or reliably predict which of the peptides comprising any 8-11 amino acids of any MMP-2 polypeptide or comprising SEQ ID NO:1, which include peptides of any length would be presented by MHC I or would be capable of inducing a cytotoxic T lymphocyte response against tumor cells expressing MMP-2.

The Federal Circuit has decided that a generic statement that defines a genus of substances by *only* their functional activity, i.e., the ability to bind MHC class I molecules, does not provide an adequate written description of the genus. See *The Reagents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997). The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is

achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

Although *Lilly* related to claims drawn to genetic material, the statute applies to all types of inventions. "Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1984 (CAFC 2004).

Additionally, "generalized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Although the skilled artisan could potentially screen peptides encompassed by the claims to identify those that are presented by MHC I and that are capable of inducing a cytotoxic T lymphocyte response against tumor cells expressing a MMP-2 polypeptide, for example, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993);

Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

"Guidelines" states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims are directed to a genus of structurally and/or functionally diverse genus of "peptides comprising any 8-11 consecutive amino acids of a MMP-2 metalloprotease" or "peptides comprising the sequence of SEQ ID NO:1" , which are capable of inducing a cytotoxic T response against tumor cells expressing an MMP-2, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. In this instance, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; Applicant has not shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; and Applicant has not described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

It is not sufficient to define a substance solely by its principal biological property, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. Per the *Enzo* court's example, (*Enzo Biochem, Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 (CA FC 2002) at 1616) of a description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) couched "in terms of its function

of lessening inflammation of tissues" which, the court stated, "fails to distinguish any steroid from others having the same activity or function". Similarly, the function of inducing a cytotoxic T response against tumor cells expressing an MMP-2, does not distinguish the claimed peptides, from others having the same activity or function and as such, fails to satisfy the written-description requirement. Applicant has not disclosed any relevant, identifying characteristics, such as structure or other physical and/or chemical properties, sufficient to show possession of the claimed genus. Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required. A description of what a material does, rather than what it is, usually does not suffice. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Given the lack of particularity with which the "immunogenic peptides comprising a T epitope presented by MHC I, that consists of a fragment of 8-11 consecutive amino acids of a structurally and functionally diverse genus of "MMP-2 metalloproteases" which are capable of inducing a cytotoxic T lymphocyte response against tumor cells expressing an "MMP-2" or with which the "immunogenic peptides comprising a T epitope, wherein the T epitope comprises the amino acid sequence of SEQ ID NO:1 which are capable of inducing a cytotoxic T lymphocyte response against tumor cells expressing an "MMP-2", to which the claims are directed, are described in the specification, it is submitted that the skilled artisan could not immediately envision, recognize or distinguish at least most of the members of this genus, to which the claims are directed; and therefore the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

16. Claims 2, 3, 5 and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the

time the application was filed, had possession of the claimed invention.

This is a NEW MATTER rejection.

In this case, in the amendment filed October 6, 2008, claim 1 has been amended to recite a peptide ... "which is capable of inducing a cytotoxic T lymphocyte response against tumor cells expressing MMP-2".

In this case, Applicant has not indicated where support occurs in the specification for this newly added limitation.

MPEP § 2163 states, "when filing an amendment an applicant should show support in the original disclosure for new or amended claims". See M.P.E.P. § 714.02 and § 2163.06. Nevertheless, as M.P.E.P. § 2163 further states: "The examiner has the initial burden of presenting evidence or reasoning to explain why persons skilled in the art would not recognize in the original disclosure a description of the invention defined by the claims. See *Wertheim*, 541 F.2d at 263, 191 USPQ at 97".

After reviewing the specification, it does not appear that the specification, including the claims, as originally filed, provide adequate support for these claims.

Notably, the specification at page 4, discloses the following:

> By way of nonlimiting example of implementation of the present invention, the inventors have identified a peptide presented by HLA-A*0201, having the sequence (l-letter code) GLPPDVQRV (SEQ ID NO: i).
>
> This peptide is capable of inducing a specific CTL response with respect to HLA-A*0201 melanoma cells expressing MMP-2, and can therefore in particular be used for obtaining medicinal products for use in the treatment of HLA-A*0201 patients.

Furthermore, at page 14, the specification teaches that only melanoma cells expressing an MMP-2 polypeptide can be recognized by cytotoxic T lymphocytes, while other tumor cells expressing an MMP-2 polypeptide are not recognized by these cytotoxic T lymphocytes.

Accordingly, it is submitted that amending the claims to recite "which is capable of inducing a cytotoxic T lymphocyte response against tumor cells expressing MMP-2" does not have written support in the specification as filed,

because it is not apparent that peptide ... "which are capable of inducing a cytotoxic T lymphocyte response against tumor cells expressing MMP-2" were originally contemplated.

Therefore, given the apparent difference in the breadth of the claims and that of the pertinent disclosures it is submitted that this clearly illustrates that such amendments have in fact introduced new concepts, thereby violating the written description requirement set forth under 35 U.S.C. §112, first paragraph.

Otherwise this issue might be resolved if Applicant were to point to other disclosures in the specification, including the claims, as originally filed, which are believed to provide the necessary written support for the language of the instant claims.

17. Claims 2, 3, 5, and 13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making and using** an isolated immunogenic peptide consisting of the amino acid sequence of SEQ ID NO:1 and compositions comprising said peptide and an adjuvant, and **while being enabling for making and using** any peptide and composition, which is encompassed by the claims and taught by the prior art, **does not reasonably provide enablement for making and using** the entire scope of the claimed invention, such as, for example, immunogenic peptides comprising the amino acid sequence of SEQ ID NO:1 that are not isolated. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can

> make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

In the instant case, the claims are broadly drawn to a genus of "immunogenic peptides comprising a T epitope presented by MHC I, that consists of a fragment of 8-11 consecutive amino acids of a genus of "MMP-2 metalloproteases", which are capable of inducing a cytotoxic T lymphocyte response against tumor cells expressing "MMP-2" (see, e.g., claim 1). Notably, due to the indefinite nature of a broad limitation followed by a narrow limitation detailed above, the claims are herein broadly, but reasonably drawn to any immunogenic peptide comprising a T epitope, wherein the T epitope consists of a fragment of 8-11 consecutive amino acids. Furthermore, claim 2 is *herein* drawn to any immunogenic peptide comprising a T epitope, wherein the T epitope comprises the amino acid sequence of SEQ ID NO:1.

Additionally, as explained in the above rejection of the claims, as failing to comply with 35 USC 101, the claims are drawn to any peptides comprising any 8-

11 amino acids of a MMP-2 metalloprotease or any peptide comprising the amino acid sequence of SEQ ID NO:1 which are not necessarily isolated.

However, the specification only provides evidence that a 9 amino acid immunogenic peptide consisting of the amino acids sequence of SEQ ID NO:1 is presented by HLA-A*0201 and is capable of inducing a specific CTL response with respect to HLA-A*0201 melanoma cells expressing an MMP-2 antigen (see e.g., page 4).

Notably, Elgert et al (Immunology: Understanding the Immune System, 1996, pages 143-145) teach that MHC class I molecules bind peptide antigens originating in cells that consist of 9-11 amino acids. Therefore, the specification does not reasonably enable the skilled artisan to make any member of the genus of peptides comprising any 8-11 amino acids of an MMP-2 or comprising the amino acid sequence of SEQ ID NO: 1, which are capable of inducing a cytotoxic T lymphocyte response because one of skill would have to practice undue and unreasonable experimentation to determine how to make and use such peptides which can be of any size that can be presented by MHC class I molecules.

Moreover, the specification does not enable the use of a peptide comprising the amino acid sequence of SEQ ID NO:1, *which is not isolated*, as one of skill in the art would be subject to undue experimentation to use such a peptide comprised in a human.

Therefore, one of skill in the art would be subject to undue experimentation to make and use the full scope of the claimed peptides, as one of skill in the art would only reasonably be able to make and use an isolated immunogenic peptide consisting of the amino acid sequence of SEQ ID NO:1 and compositions comprising said peptide and an adjuvant.

Applicant is reminded that reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea

does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Claim Rejections - 35 USC § 102

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

19. Claims 2, 3, 5 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent 5,763,219 (Keyomarsi, 1996).

In this case, due to the indefinite nature of the claims as detailed above, the claims are herein drawn to immunogenic peptides comprising a T epitope presented by MHC I, wherein the T epitope consists of 8-11 consecutive amino acids of an MMP-2 metalloproteinase. Notably, because it is unclear what must be capable of inducing a cytotoxic T lymphocyte response against tumor cells expressing MMP-2, the claims are broadly, but reasonably being interpreted to include any structurally and materially indistinguishable peptide. Furthermore,

claim 2 is herein drawn to any immunogenic peptide comprising a T epitope, wherein the T epitope comprises the amino acid sequence of SEQ ID NO:1. Claims 5 and 13, are further drawn to a composition comprising a peptide of claim 2 or 3 respectively and an adjuvant. Notably, because the specification does not expressly define the term adjuvant, the scope of the claims is being interpreted in light of the definition provided by Dorland's Medical Dictionary which defines adjuvant as "assisting or aiding. a substance which aids another"[1] Copyright © 2002-2008 Merck & Co., Inc., All rights reserved. In light of this definition, the compositions are broadly, but reasonable interpreted to include any composition of the peptide in a buffer, since one of skill in the art would recognize that a buffers are substances which inherently aid a peptide in some manner, e.g., stability, solubility, activity, etc.

Keyomarsi teaches immunogenic peptides comprising a random decapeptide library (10 amino acids in length) and immunogenic peptides comprising a random dodecapeptide library (12 amino acids in length) and compositions comprising such libraries in buffers, wherein the peptides comprise any of the naturally occurring amino acids at each position which are produced using random synthetic oligonucleotides (see page 26, lines 15-29). Accordingly, Keyomarsi inherently teaches immunogenic peptides comprising a T epitope presented by MHC I, wherein the T epitope consists of 8-11 consecutive amino acids of an MMP-2 metalloproteinase and immunogenic peptides comprising a T epitope, wherein the T epitope comprises the amino acid sequence of SEQ ID NO:1 because any T epitopes of 8-11 amino acids in a MMP-2 metalloproteinase would inherently be comprised within the random decapeptide library and/or the random dodecapeptide of Keyomarsi. Therefore, the peptides and compositions disclosed by Keyomarsi are materially and structurally indistinguishable from the instantly claimed peptides. Thus, absent a showing of any difference, the claimed peptides and the peptides disclosed by the prior art are deemed the same.

[1] See Exhibit A

20. Claims 2, 3, 5 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent No. 6,500,924 (Brooks et al, 2002).

In this case, due to the indefinite nature of the claims as detailed above, the claims are herein drawn to immunogenic peptides comprising a T epitope presented by MHC I, wherein the T epitope consists of 8-11 consecutive amino acids of an MMP-2 metalloproteinase. Notably, because it is unclear what must be capable of inducing a cytotoxic T lymphocyte response against tumor cells expressing MMP-2, the claims are broadly, but reasonably being interpreted to include any structurally and materially indistinguishable peptide. Furthermore, claim 2 is herein drawn to any immunogenic peptide comprising a T epitope, wherein the T epitope comprises the amino acid sequence of SEQ ID NO:1. Claims 5 and 13, are further drawn to a composition comprising a peptide of claim 2 or 3 respectively and an adjuvant. Notably, because the specification does not expressly define the term adjuvant, the scope of the claims is being interpreted in light of the definition provided by Dorland's Medical Dictionary which defines adjuvant as "assisting or aiding. a substance which aids another" In light of this definition, the composition are broadly, but reasonable interpreted to include any composition of the peptide in a buffer, since one of skill in the art would recognize that a buffers are substances which inherently aid a peptide in some manner.

Brooks et al teach an immunogenic peptide that comprises the amino acid sequence of SEQ ID NO:20, which comprises the amino acid sequence of the instantly recited SEQ ID NO:1, and compositions comprising said peptide in buffers (see entire document, e.g., SEQ ID NO:20, alignment attached as Exhibit B and columns 15-20). Accordingly, Brooks et al teach immunogenic peptides comprising a T epitope presented by MHC I, wherein the T epitope consists of 8-11 consecutive amino acids of an MMP-2 metalloproteinase and immunogenic peptides comprising a T epitope, wherein the T epitope comprises the amino acid sequence of SEQ ID NO:1. Therefore, the peptides and compositions disclosed

by Brooks et al are materially and structurally indistinguishable from the instantly claimed peptides. Thus, absent a showing of any difference, the claimed peptides and the peptides disclosed by the prior art are deemed the same.

21. Claims 2 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by WO/2002/098351 (Brooks et al, 2002, cited by Applicant; IDS filed 3/14/2006).

In this case, due to the indefinite nature of the claims as detailed above, the claims are herein drawn to immunogenic peptides comprising a T epitope presented by MHC I, wherein the T epitope consists of 8-11 consecutive amino acids of an MMP-2 metalloproteinase. Notably, because it is unclear what must be capable of inducing a cytotoxic T lymphocyte response against tumor cells expressing MMP-2, the claims are broadly, but reasonably being interpreted to include any structurally and materially indistinguishable peptide. Claim 5 is further drawn to a composition comprising a peptide of claim 2 and an adjuvant. Notably, because the specification does not expressly define the term adjuvant, the scope of the claims is being interpreted in light of the definition provided by Dorland's Medical Dictionary which defines adjuvant as “assisting or aiding. a substance which aids another” In light of this definition, the composition are broadly, but reasonable interpreted to include any composition of the peptide in a buffer, since one of skill in the art would recognize that a buffers are substances which inherently aid a peptide in some manner.

WO/2002/098351 teaches an immunogenic peptide of an MMP-2 polypeptide that has the amino acid sequence of Ile-Phe-Ala-Gly-Asp-Lys-Phe-Trp-Arg and compositions comprising said peptide in buffers (see entire document, e.g., page 3). While WO/2002/098351 does not assay the peptide to determine that such a peptide is a T epitope presented by MHC I, because the peptide of WO/2002/098351 is a 9-mer fragment of a MMP-2 polypeptide as is recited in the claims, the peptide and compositions disclosed by WO/2002/098351 are materially and structurally indistinguishable from the

instantly claimed peptides and compositions. Notably, the Office lacks the resources and facilities to determine whether the peptide of WO/2002/098351 comprises a T epitope presented by MHC I. Consequently, in the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed peptides and compositions are different from the peptides and compositions taught by the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA, 1977); and *Ex parte Gray*, 10 USPQ2d 1922 1923 (PTO Board of Patent Appeals and Interferences, 1988 and 1989).

Allowable Subject Matter

22. It is submitted that a claim drawn to an isolated immunogenic peptide consisting of the amino acid sequence of SEQ ID NO:1, which is apparently not taught or fairly suggested by the prior art, would be allowable, as the claimed subject matter would meet the requirements set forth under 35 U.S.C. §§ 101, 102, 103, and 112, first paragraph, as having been adequately described in the instant application to satisfy both the written description and enablement provisions.

Conclusion

23. No claim is allowed.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached at Monday through Friday from 7:00 AM to 4:30 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public

PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
Brad Duffy
571-272-9935

/Stephen L. Rawlings/
Primary Examiner, Art Unit 1643

/bd/
Examiner, Art Unit 1643
January 2, 2008